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Editorial and study commentary by Dr Angela George

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Dr George has authored multiple peer-reviewed publications and book chapters and undertakes a variety of clinical and translational research projects, particularly in cancer genomics and targeted treatments.

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Abbreviations used in this issue

AKI = a serine/threonine protein kinase
ASCO = American Society of Clinical Oncology
BRCA = breast cancer gene
CCND1 = cyclin D1
CI = confidence interval
CNS = central nervous system
ER = estrogen receptor
ESCAT = ESMO Scale for Clinical Actionability of molecular Targets
ESMO = European Society for Medical Oncology
FDG-PET = fluorodeoxyglucose-positron emission tomography
FGFR1 = fibroblast growth factor receptor 1
FISH = fluorescence in situ hybridisation
FOLFOX = leucovorin, fluorouracil, and oxaliplatin
FOLFOXIRI = leucovorin, fluorouracil, oxaliplatin, and irinotecan
HER2 = human epidermal growth factor receptor 2
HR = hazard ratio
HRD = homologous recombination deficient
IHC = immunohistochemistry
KRAS = Kirsten rat sarcoma viral oncogene homolog
MMR = mismatch repair
MRI = magnetic resonance imaging
NSCLC = non-small-cell lung cancer
NTRK = neurotrophic tyrosine receptor kinase
ORR = objective response rate
OS = overall survival
PARP = poly-ADP ribose polymerase
PD1 = programmed death 1
PD-L1 = programmed death ligand 1
PFS = progression-free survival
PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
RR = relative risk
TRAEs = treatment-related adverse events

Comprehensive Genomic Profiling and Informed Decision-Making

As we celebrate the first anniversary of *Perspectives on Precision Oncology Research Review*, we plan to review some of the guidelines that are currently helping to frame the way in which we undertake and utilise the wealth of genomic information that is currently available. As more patients have large panels performed, there is a risk that they may be found to have multiple potentially targetable genomic alterations, with little guidance to suggest the order in which we should select drugs that will target these. This is a particular issue with many of the commercially available somatic tests, which will often list potential drugs that are available in the country in which the testing was undertaken (e.g., USA) alongside any mutations identified. These drugs may not be available or therapeutically beneficial in the tumour type of the patient, leading to confusion or disappointed patients. It is therefore vital to consider ways to apply the available evidence to these alterations to help determine which tests are most important and which results should be prioritised in the treatment pathway. With this in mind, we are starting with the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[1]

ESMO Scale for Clinical Actionability of molecular Targets

ESCAT is a classification system that was initially proposed by ESMO in 2018 as a way of ranking genomic alterations into different tiers of clinical utility based on the available evidence. It was envisaged that this could be applied both by pharma stakeholders for drug development and by clinicians setting up clinical studies to prioritise molecular findings and match patients with appropriate drugs. It is expected that the specific classification for any alteration may alter by tumour type. For example, a tumour *BRCA* mutation would occupy a different tier for those with ovarian cancer compared to those with the same mutation and cervical cancer due to the different clinical implications for each patient. It is also expected that targets will change tiers as more evidence becomes available.

ESCAT has six tiers, ranging from Tier I (suitable for routine use), Tier II (investigational at present), Tiers III and IV (hypothetical target based on other tumour type or preclinical evidence, respectively), Tier V (active drug but no evidence of clinical benefit), and Tier X (lack of evidence for actionability). There are subgroups within each tier based on the specific level of evidence, including the type of trial that the agent has been used in. Since first being proposed, we are increasingly seeing the use of the ESCAT system as a stratifying tool in early phase or molecular matching trials to help select the most appropriate mutations to target.

This has led to a number of individual publications by various tumour types, laying out the current frequently identified targets by tumour type and their relative importance, such as the paper by Condorelli et al., in breast cancer.[2] This paper lays out the 40 recurrently mutated driver alterations frequently reported in breast cancer in order of importance for treatment, with HER2 amplification, germline *BRCA1/2* and somatic *PIK3CA* mutations, and NTRK fusions all allocated to Tier I based on current knowledge. Thus, a patient found to have mutations in *PIK3CA*, *AKT*, *CCND1*, *HER2* and *FGFR1* would have these ranked in order of evidence for targeting as:

Tier 1: *PIK3CA*
Tier II: *AKT*
Tier III: *HER2* mutations (as opposed to HER2 amplification which is Tier I)
Tier X: *CCND1* and *FGFR1*

The ESCAT classification system provides a systematic framework to rank molecular targets based on clinical evidence of actionability.[1]

	ESCAT Evidence Tier	
Suitable for Routine Use	Tier I	
Investigational	Tier II	
Hypothetical Target	Tier III	Tier IV
Combination Development	Tier V	
Lack of Evidence	Tier X	

These guidelines allow clinicians who might not be as familiar with all of the different mutations that may be present in a tumour to be able to sift through the results and choose the best first treatment. It can also help differentiate between driver and passenger mutations for a specific tumour type by ranking the various genomic alterations.

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Precision Oncology at ASCO 2022

Following on from the ESCAT guidelines, there are also a number of full papers that have been published recently from the huge number of presentations of precision oncology studies at the ASCO 2022 conference. The first of these is the DESTINY-Breast04 trial of trastuzumab deruxtecan in patients with previously treated HER2-low advanced breast cancer by Modi et al. (which would be ESCAT Tier X).[3] This study randomised patients found to be HER2 1+ or 2+ on IHC (with negative FISH) to receive either physician's choice of chemotherapy (including eribulin, capecitabine, paclitaxel, nab-paclitaxel or gemcitabine) or trastuzumab deruxtecan. The results showed an ORR of 52.3% in the trastuzumab group compared with 16.3% in the chemotherapy group, with very similar rates in both the hormone receptor-positive and hormone receptor-negative subgroups. There was a corresponding and statistically significant improvement in both PFS and OS in patients treated with trastuzumab deruxtecan compared with chemotherapy, suggesting that trastuzumab deruxtecan provides an additional treatment option in the many patients with HER2-low disease who would not previously have been considered for this approach.

BRCA1/2 mutations are an ESCAT Tier I mutation in high-grade serous ovarian cancer

BRCA1/2 mutations are an ESCAT Tier I mutation in high-grade serous ovarian cancer, with evidence for their routine use as a maintenance treatment in both first and subsequent lines of treatment.[1] In addition to the SOLO1 and PRIMA studies of olaparib and niraparib, respectively, in first-line maintenance treatment, we now have the ATHENA study of rucaparib to add to the mix.[4-6] Like the PRIMA study, the ATHENA trial stratified patients based on homologous recombination status (deficient [HRD] vs proficient) then randomised them 4:1 to either rucaparib or placebo. Of note, this study also included patients from New Zealand. There was a clear improvement in median PFS in HRD patients treated with rucaparib as maintenance treatment (28.7 months vs 11.4 months in the placebo group). In all-comers, median PFS was 9.2 months compared with 20.2 months in the placebo group. As a group, PARP inhibitors have a number of shared class toxicities, but each agent within this class also has some unique side effects. This means that there is now the possibility of choosing the individual PARP inhibitor that may best suit each patient. Those with an underlying *BRCA* mutation could potentially choose from all three, whilst the remaining patients could be treated with either rucaparib or niraparib.

Lung cancer now has a number of ESCAT Tier I and II mutations that can be utilised in the optimal treatment of patients with advanced disease.[1] One of the most important mutations that has been able to be targeted in the last few years has been the 'death star' mutation, otherwise known as the *KRAS*^{G12C} mutation. This mutation is the driver mutation in about 14–20% of NSCLCs, and is also found in those with both upper and lower gastrointestinal tumours, where it indicates a universally poor outcome. The development of sotorasib has been a huge step forward in being

One of the most important mutations that has been able to be targeted in the last few years has been the 'death star' mutation, otherwise known as the KRAS ^{G12C} mutation

able to improve outcomes for these patients, and now we have an additional treatment option, based on data from a phase II study of adagrasib, as reported by Jänne et al., in the NEJM.[7,8] Of most interest in this study are the 33 patients with previously treated brain metastases, of whom 11 (33%) had an objective intracranial response. This is a particularly difficult-to-treat group, therefore this brings new hope for these patients.

Moving from lung to colorectal cancer, we have the TRIPLETE study in those with *RAS/BRAF* wildtype metastatic colorectal cancer.[9] This study compared the standard FOLFOX regimen of fluorouracil, leucovorin and oxaliplatin with FOLFOXIRI (FOLFOX with the addition of irinotecan), both with panitumumab added in. Again, *RAS* and *BRAF* are ESCAT Tier I mutations in colorectal cancer, where their presence or absence indicates benefit or otherwise with targeted agents such as cetuximab or panitumumab. In the TRIPLETE study, the addition of irinotecan was assessed to see if this would improve the ORR and PFS given that this drug has established activity in colorectal cancer and is often the backbone of second-line chemotherapy for relapsed patients. FOLFOXIRI is also commonly used in those with advanced pancreatic cancer, particularly patients who may be down-staged and able to undergo surgical resection following chemotherapy, but this comes at the expense of significant side effects. In TRIPLETE, no significant difference in objective response, chance of complete resection or PFS was seen with the addition of irinotecan, although there was an increase in the rate of Grade 3 or 4 toxicity (from 57% to 69%). Based on this study, there is no justification to add in irinotecan to standard FOLFOX/panitumumab at present.

…we now have evidence to consider the use of PD-1 inhibitors in the 5–10% of rectal cancers that are MMR deficient

When we think of mismatch repair (MMR) in colorectal cancer, another ESCAT Tier I target, we generally think of right-sided bowel tumours. We have clear evidence for the use of PD-L1 inhibitors in these patients from a number of immunotherapy studies.[10] However, thanks to Cercek and colleagues, we now have evidence to consider the use of PD-1 inhibitors (in this case dostarlimab) in the 5–10% of rectal cancers that are MMR deficient.[11] In this small study (only 12 patients to date) of patients with locally advanced disease, there was a complete response after treatment with neoadjuvant dostarlimab for up to 6 months. The disease remained resolved at least 6 months later. The idea that these patients could forgo chemoradiation or surgery is extraordinary, and requires confirmation both in a larger study and with longer follow-up. It is also not clear why these patients responded so much more completely than those with metastatic colorectal cancer that is MMR deficient, but this is a hugely exciting study that may well lead to similar results in other MMR-deficient tumours.

Looking Ahead

The world of precision medicine continues to evolve as the number of drugs and potential targets expands rapidly. Our next issue will focus on the exponential rise of circulating tumour DNA, both in the diagnosis and prognosis of malignancies, as well as disease tracking to allow selection of patients who require adjuvant chemotherapy. This is rapidly gaining traction in ascertaining those who have minimal residual disease likely to recur, providing the opportunity to intervene before macroscopic disease relapse occurs. We look forward to reviewing the evidence for this approach and assessing which aspects of this are ready for prime time.

We hope that you find this editorial and these articles of academic or clinical interest and welcome any feedback.

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REFERENCES:

References in bold are summarised with additional commentary in our Key Publication Summaries Section.

1. **Mateo J et al. A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018;29(9):1895-1902**
2. **Condorelli R et al. Genomic alterations in breast cancer: Level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2019;30(3):365-373**
3. **Modi S et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9-20**
4. Moore K et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. 2018;379(26):2495-2505
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6. **Monk BJ et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol. 2022; Jun 6 [Epub ahead of print]**
7. Skoulidis F et al. Sotorasib for lung cancers with *KRAS p.G12C* mutation. N Engl J Med. 2021;384(25):2371-2381
8. **Jänne PA et al. Adagrasib in non-small-cell lung cancer harboring a *KRAS^{G12C}* mutation. N Engl J Med. 2022;Jun 3 [Epub ahead of print]**
9. Rossini D et al. Upfront modified fluorouracil, leucovorin, oxaliplatin, and irinotecan plus panitumumab versus fluorouracil, leucovorin, and oxaliplatin plus panitumumab for patients with *RAS/BRAF* wild-type metastatic colorectal cancer: The phase III TRIPLETE study by GONO. J Clin Oncol. 2022;Jun 6 [Epub ahead of print]
10. Jin Z and Sinicrope FA. Mismatch repair-deficient colorectal cancer: Building on checkpoint blockade. J Clin Oncol. 2022;Jun 1 [Epub ahead of print]
11. **Cercek A et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med. 2022;Jun 5 [Epub ahead of print]**

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KEY PUBLICATION SUMMARIES

A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

Authors: Mateo J et al.

Summary: The ESMO Translational Research and Precision Medicine Working Group undertook a collaborative project to develop a genomic alteration classification system identifying their value as clinical targets. The first version of the ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) uses six levels of clinical evidence for molecular targets: I - targets for use in routine clinical decisions; II - investigational targets that may define a patient population benefiting from a targeted drug but requiring additional research; III - clinical benefit in other tumours or similar molecular targets; IV - preclinical evidence of value; V - evidence for co-targeting approaches; X - lacking evidence.

Comment: This article outlines the original ESCAT classification system, which is increasingly being used in molecular matching trials and drug development protocols to identify the most important mutations in each tumour type. The paper outlines not only the six major categories but also the subcategories, based on the level of trial evidence available. While this is likely to be revised and updated as more possible categories are considered, the original guidelines are currently those in use for clinicians to guide the choice of treatment.

Reference: Ann Oncol. 2018;29(9):1895-1902
Abstract

Genomic alterations in breast cancer: Level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

Authors: Condorelli R et al.

Summary: This ESCAT-based assessment of genomic alterations observed in breast cancer was performed to help clinicians to prioritise treatment. Database analysis suggested around 40 recurrent breast cancer driver alterations. Tier of evidence IA included *ERBB2* amplification, germline *BRCA1/2* mutations, and *PIK3CA* mutations based on large, randomised trials demonstrating anti-tumour activity of targeted therapies. Tier IC included *NTRK* fusions and microsatellite instability. Tier IIA included *ESR1* mutations and *PTEN* loss, while tier IIB included *ERBB2* and *AKT1* mutations. Tier III included somatic *BRCA1/2* mutations, *MDM2* amplifications and *ERBB3* mutations. Tier IV included 17 genes based on preclinical evidence. Tier X alterations included *FGFR1* and *CCND1*.

Comment: This paper provides an example of the ESCAT system in use, in this case classifying the recurrent mutations identified in breast cancer. Similar publications exist across a wide range of tumour types for individual clinicians to use when considering which molecular targets should be prioritised for their patient based on the evidence available at the time.

Reference: Ann Oncol. 2019;30(3):365-373
Abstract

Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer

Authors: Modi S et al.

Summary: The randomised controlled phase III DESTINY-Breast04 trial assessed the response to treatment with trastuzumab deruxtecan or physician's choice chemotherapy in 557 patients with HER2-low (1+ IHC analysis or IHC 2+ and negative FISH) metastatic breast cancer after 1–2 previous chemotherapy regimens. Overall, 494 patients (88.7%) were hormone receptor-positive and 63 (11.3%) were hormone receptor-negative. Among hormone receptor-positive patients, median PFS was 10.1 months in those treated with trastuzumab deruxtecan and 5.4 months in those treated with physician's choice therapy (HR 0.51; $p < 0.001$); corresponding median OS in the two groups was 23.9 versus 17.5 months (HR 0.64; $p = 0.003$). In the overall study population, median PFS was 9.9 months versus 5.1 months (HR 0.50; $p < 0.001$) and median OS was 23.4 versus 16.8 months (HR 0.64; $p = 0.001$). Grade ≥3 adverse events were observed in 52.6% of patients treated with trastuzumab deruxtecan and 67.4% of those receiving physician's choice therapy. Drug-related interstitial lung disease or pneumonitis and Grade 5 adverse events occurred in 12.1% and 0.8% of trastuzumab deruxtecan recipients, respectively.

Comment: To date, we have saved the HER2-targeting antibodies such as trastuzumab and pertuzumab for those who have HER2 3+ on IHC, or a positive FISH test. These patients, with clear amplification of HER2, generally have more aggressive tumours and an otherwise poorer outcome without this treatment compared to those with HER2-negative tumours. However, the results of this study now suggest that any HER2-expressing tumours might benefit from trastuzumab, opening up additional treatment and maintenance therapy options to those who would previously not have been considered for this. The rate of interstitial lung disease, however, was not insignificant, nor is the increased risk of cardiotoxicity seen with trastuzumab deruxtecan, especially because all patients are likely to have received prior anthracycline-based treatment.

Reference: N Engl J Med. 2022;387(1):9-20
Abstract

A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA–MONO/ GOG-3020/ ENGOT-ov45)

Authors: Monk BJ et al.

Summary: The randomised, placebo-controlled, phase III ATHENA trial assessed the use of rucaparib as first-line maintenance therapy in 538 patients with Stage III-IV high-grade ovarian cancer undergoing surgical cytoreduction. This included patients without *BRCA1* or *BRCA2* mutations or other evidence of homologous recombination deficiency, or high-risk clinical characteristics such as residual disease. In the intent-to-treat population, median PFS was 20.2 months (95% CI 15.2–24.7) in the rucaparib group versus 9.2 months (95% CI 8.3–12.2) in the placebo group (HR 0.52; 95% CI 0.40–0.68; p = 0.0001). In HRD patients, median PFS was 28.7 months (95% CI 23.0–not reached) versus 11.3 months (95% CI 9.1–22.1) in those treated with rucaparib versus placebo, respectively (HR 0.47; 95% CI 0.31–0.72; p = 0.0004); corresponding values in HRD-negative patients were 12.1 months (95% CI 11.1–17.7) versus 9.1 months (95% CI 4.0–12.2; HR 0.65; 95% CI 0.45-0.95). The most common Grade ≥3 TRAEs in the rucaparib and placebo groups were anaemia (28.7% vs 0%) and neutropenia (14.6% vs 0.9%).

Comment: Responses to rucaparib in this study were very similar to those to niraparib in the PRIMA study. In the above study, around 21% of patients had *BRCA* mutations, 22% had other HRD mutations, 44% were homologous recombination proficient and around 12% were homologous recombination status unknown. Of note, homologous recombination status for the ATHENA study was assessed by the Foundation Medicine HRD test, which is not currently commercially available and is slightly different to the available Myriad HRD test, so the two populations are not completely interchangeable. There was still benefit noted with rucaparib in the homologous recombination proficient population, with an HR of 0.65 for the between-group comparison compared to 0.58 in the HRD population and 0.40 in *BRCA*-mutated patients. This study is likely to improve choice for patients in the first-line maintenance setting, but also indicates that we should be stratifying all of these patients by homologous recombination status when selecting the best maintenance treatment from a PARP inhibitor, bevacizumab or both.

Reference: J Clin Oncol. 2022;Jun 6 [Epub ahead of print]
Abstract

Adagrasib in non-small-cell lung cancer harboring a *KRAS*^{G12C} mutation

Authors: Jänne PA et al.

Summary: In this phase II study, 112 patients with *KRAS*^{G12C}-mutated NSCLC received the *KRAS*^{G12C} inhibitor adagrasib after platinum-based chemotherapy and anti-PD1 or anti-PD-L1 therapy. Over a median follow-up of 12.9 months, the ORR rate was 42.9% (primary endpoint assessed by blinded independent central review). Median response duration was 8.5 months (95% CI 6.2–13.8) and median PFS was 6.5 months (95% CI 4.7–8.4). After a median follow-up of 15.6 months, the median OS was 12.6 months (95% CI 9.2–19.2). In the subgroup with CNS metastases (n=33), the intracranial ORR was 33.3% (95% CI 18.0–51.8). TRAES occurred in 97.4% of patients. These were Grade 1-2 severity in 52.6% and Grade ≥3 in 44.8%, and 6.9% of patients discontinued treatment due to TRAEs.

Comment: There is a particular need to improve outcomes in NSCLC patients with brain metastases. As each new generation of targeted treatments has come through, agents that cross the blood/brain barrier or can target mechanisms of resistance, such as osimertinib, have improved outcomes. Sotorasib was the first drug to be able to target the *KRAS*^{G12C} mutation that is associated with a particularly bad outcome, but isn't fantastic at targeting brain metastases, with only a 13% response rate in intracranial disease. Although only a phase II study, the 33% response in intracranial disease with adagrasib is very promising and, if confirmed in larger studies, could be a real step forward for treatment.

Reference: N Engl J Med. 2022;Jun 3 [Epub ahead of print]
Abstract

PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer

Authors: Cercek A et al.

Summary: This prospective phase II study assessed the use of an anti-PD-1 monoclonal antibody, dostarlimab, every 3 weeks for 6 months in 12 patients with mismatch repair-deficient Stage II or III rectal adenocarcinoma. A clinical complete response was observed in all patients (95% CI 74-100%), with no evidence of tumour on MRI, ^{18}FDG-PET, endoscopic evaluation, digital rectal examination, or biopsy. There was no progression or recurrence during 6–25 months' follow-up and no adverse events of Grade ≥3.

Comment: This is a landmark study that could totally change our treatment of Stage II and III rectal cancer in those with MMR deficiency. This is a small study, and there will be a degree of patient selection bias. However, even keeping this in mind, the results emphasise the need to test all colorectal cancers for MMR, not just right-sided tumours, because there are a proportion of rectal tumours that are MMR deficient. By identifying these patients, we could give them the opportunity to potentially avoid the long-term effects of radiotherapy and surgery, including a stoma. These findings require confirmation in a larger study, but they are a hugely exciting step forward in rectal cancer management in the subgroup population.

Reference: N Engl J Med. 2022;386:2363-2376
Abstract